Published in final edited form as:

Clin Cancer Res. 2017 February 01; 23(3): 658–665. doi:10.1158/1078-0432.CCR-16-0940.

Skeletal Muscle Measures as Predictors of Toxicity, Hospitalization, and Survival in Patients with Metastatic Breast Cancer Receiving Taxane Based Chemotherapy

Shlomit Strulov Shachar, MD[1,2], **Allison M. Deal, MS**[1], **Marc Weinberg, PhD**[1], **Kirsten A. Nyrop, PhD**[1], **Grant R. Williams, MD**[1], **Tomohiro F. Nishijima, MD**[1], **Julia M. Benbow, BA**[1], and **Hyman B. Muss, MD**[1]

[1]UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

[2]Division of Oncology, Rambam Health Care Campus, Haifa, Israel

Abstract

Purpose—Severe skeletal muscle (SM) loss (sarcopenia), is associated with poor cancer outcomes including reduced survival and increased toxicity. This study investigates SM measures in metastatic breast cancer (MBC) patients receiving first line taxane-based chemotherapy and evaluates associations with treatment toxicity and other outcomes.

Experimental Design—Using computerized tomography (CT) images taken for the evaluation of disease burden, skeletal muscle area (SMA) and density (SMD) were measured at the 3rd lumbar vertebrae. Sarcopenia was defined as Skeletal Muscle Index (SMI=SMA/height^2) ≤41. Skeletal Muscle Gauge (SMG) was created by multiplying SMI x SMD. Fisher's exact tests, t-tests, the Kaplan-Meier method, and Cox regression modeling were used.

Results—MBC patients (N=40), median age 55 (rang 34–80), 58% sarcopenic, median SMG 1296 AU (SD 522). Grade 3–4 toxicity was found in 57% of sarcopenic vs 18% of non-sarcopenic patients (p=0.02). Toxicity-related hospitalizations were also higher in sarcopenic patients (39% vs 0%, p=0.005) as were any adverse events -- defined as any grade 3–4 toxicities, hospitalizations, dose reductions, or dose delay -- (74% vs 35%, p=0.02). Low SMG was associated with grade 3–4 toxicity (p=0.04), hospitalization (p=0.01) and time to treatment failure (for progression or toxicity) (p=0.03). Low SMG had a borderline significant association with any adverse event (p=0.06) and overall survival (p=0.07).

Conclusions—SM measures are associated with toxicity outcomes and survival in MBC patients receiving first line taxane-based chemotherapy. Further studies are needed to explore how routinely obtained CT scans can be used to individualize dosing and improve treatment planning.

Keywords

metastatic breast cancer; sarcopenia; muscle attenuation; skeletal muscle index; skeletal muscle gauge; hospitalizations; toxicity; survival; taxane chemotherapy

*Corresponding author: Shlomit Strulov Shachar, Address; 170 Manning Drive, Campus Box 7305 Chapel Hill NC 27599, USA. s_shachar@rambam.health.gov.il, Phone; +1-919-966-2891, Fax numbers;+1-919-627-3221.

Conflict of interest: none

Introduction

With over 1.5 million new cases per year, breast cancer is the most common cancer and leading cause of cancer mortality in women worldwide (1). In the U.S. in 2016, there will be an estimated 246,660 new cases of breast cancer and 40,450 breast cancer deaths, most of them due to metastatic disease (2). Six to ten percent of new metastatic breast cancer (MBC) cases are diagnosed as “de novo” Stage IV and an estimated 20–30% of all existing breast cancer cases will have metastatic recurrence (3). When distant metastasis are diagnosed, breast cancer is incurable with a median survival of 2 to 3 years (4). Chemotherapy is an essential component of treatment for MBC and toxicity prediction is an important challenge in oncology practice.

The term sarcopenia was described by Baumgartner *et al* to describe age-related loss of muscle mass in older adults (5). He developed an index of relative muscle mass calculated as the appendicular skeletal muscle mass, measured by dual-energy x-ray absorptiometry (DEXA). More recently, sarcopenia research in oncology has focused on technology that uses widely available computed tomographic (CT) imaging (6) that is used for staging, surveillance, and assessing tumor response in patients with cancer.

Sarcopenia is a commonly observed in patients with advanced cancer. In a recent meta-analysis, 19–74% of patients with advanced solid tumors were sarcopenic, and the presence of sarcopenia was correlated with poor overall survival (OS) (Hazzard ratio (HR)=1.44, $p<0.001$)(6). Prado *et al* found a significant association between sarcopenia and capecitabine toxicity in MBC patients. Pre-existing sarcopenia was associated with toxicity in 50% of patients compared to 20% who were non sarcopenic ($p=0.03$); time to tumor progression (TTP) was also shorter for sarcopenic vs non-sarcopenic patients (101 versus 173 days, respectively; $p=0.05$) and had an independent effect on TTP in multivariate model (HR= 2.6; $p=0.01$) (7). In an Asian study of early breast cancer patients, which examined the association between body composition and toxicity from doxorubicin, it was shown that higher increased visceral fat was significantly associated with grade 4 leukopenia ($p=0.014$) (8). These findings suggest that different body composition measures may be a predictor of chemotherapy toxicity.

To further explore the potential role of sarcopenia as a predictor of toxicity and other adverse clinical outcomes we studied patients with metastatic breast cancer who had first line chemotherapy with taxanes and who had baseline CT that allowed for measurement of muscle mass. We chose taxanes as these are among the most widely used and effective agents in this setting (9, 10). The purpose of this study was to investigate if skeletal muscle and body composition measures - body surface area (BSA), body mass index (BMI), lean body mass (LBM), skeletal muscle density (SMD), and a novel measure of skeletal muscle gauge (SMG) were associated with chemotherapy toxicity, hospitalizations, dose delays or reductions, time to treatment failure, and overall survival.

Patients and Methods

Participants

To be eligible for this study, patients needed to be female, age 21 or older, and receiving chemotherapy for MBC at the University of North Carolina (UNC) Cancer Hospital. Patients had to be undergoing the following commonly-used first line taxane-containing chemotherapy regimens: paclitaxel, docetaxel, or *nab*-paclitaxel. Patients with any histological type, grade, hormone receptor status, or HER-2 status were eligible. Patients also had to have a CT scan of the abdomen dating no more than 45 days prior to chemotherapy initiation with digital images available for muscle mass assessment and complete medical records at UNC. Eligible patients were identified through a review of patients in the IRB-approved UNC Metastatic Breast Cancer Clinical Database. There was no direct contact with patients, as all data were collected through registry and electronic medical records. The study was approved by the UNC Institutional Review Board.

Toxicity grading and measures

Toxicity grades 3–5 according to National Cancer Institute Common Toxicity Criteria for adverse events (11) (NCI- CTCAE) (Version 4.03) were captured from the electronic medical record (EMR). We specifically focused our chart review on hematologic toxicity (neutropenia, thrombocytopenia, anemia), febrile neutropenia, white blood cell growth factor (G-CSF) usage, neurotoxicity, gastrointestinal toxicity (stomatitis, diarrhea, vomiting), dose reductions and treatment delays, hospitalizations due to chemotherapy toxicity, and death. If there was any uncertainty concerning hospitalization due to treatment toxicity, a second medical oncologist reviewed the charts and the patient's cause of hospitalization was adjudicated by consensus. A composite variable of "any adverse event" was defined as any hospitalization, grade 3–4 toxicity, dose reductions, or dose delay. Time to treatment failure (TTF) was defined as days from start to end of chemotherapy whether stopped for either toxicity or tumor progression. OS was defined as the time in years from chemotherapy initiation to either death or last date of contact.

Other measures

In addition to toxicity data, we also collected age at diagnosis of metastasis, disease free interval, hormone receptor (HR) subtype, metastatic sites, whether a biologic agent was used with chemotherapy, the type of taxane chemotherapy, BSA, BMI, and prior hormonal therapy (if used).

BMI was calculated using the following formula: BMI = weight (kg)/height^2 (m^2). Classification of obese referred to patients with BMI ≥30.0 kg/m^2. BSA was calculated using: $\mathrm{BSA}\ (\mathrm{m}^2) = \sqrt{\left[\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}\right]}$.

CT-based body composition measures

Abdominal CT images were acquired from the UNC Picture Archiving and Communication System office and analyses were conducted with the guidance of a faculty radiologist. CT images were examined using Impax radiological software (AGFA-version 6, Morstel,

Belgium) and transverse sections at the level of L3 were extracted for our analyses. L3 lumbar segments were processed using automated image segmentation software,(12, 13) The software recognizes muscle tissue based on density threshold between −29 and +150 HU, while using *a priori* information about the L3 muscle shape to avoid mislabeling parts of the neighboring organs that also have HU values in the −29 +150 range. The program provides a highly accurate, unbiased estimation of the cross-sectional lean tissue area and skeletal muscle area. Skeletal muscle index (SMI) was calculated using the following formula -- (L3-muscle area-cm^2)/(patient height-m^2) (14). An SMI of 41 or less was considered sarcopenic based on previously derived optimal stratification statistics relating SMI to increased mortality in a large population of patients with colorectal and lung cancer (14). Estimation of LBM was calculated using the formula (7) (LBM (kg) = [(L3 Muscle measured by CT (cm2) × 0.3) + 6.06]).

Mean SMD was derived by averaging Hounsfield Units (HU) of skeletal muscle at the L3 vertebrae. The attenuation of skeletal muscle is used as a non-invasive radiological technique to indirectly assess muscle fat content. The density of skeletal muscle is inversely related to muscle fat content [(15)]. Since SMI and SMD are each significantly associated with outcome (6, 16, 17), we explored whether combining the two skeletal muscle measures together resulted in stronger correlations with outcomes. To integrate both skeletal muscle quantity (SMI) and skeletal muscle density (SMD), we used the “skeletal muscle gauge” (SMG) by multiplying SMI x SMD first presented by Weinberg *et al.* The actual units for SMG are: (cm^2 tissue * average HU)/(m^2 height) for simplicity we chose to represent them as arbitrary units (AU)(18) (see Figure 1).

Statistical analysis

Fisher’s exact and two group t-tests were used evaluate associations between body composition measures and toxicity. The Kaplan-Meier method was used to estimate median times, and univariable Cox regression modeling was used to estimate hazard ratios and compare TTF and OS. A p-value of <= .05 was considered statistically significant. To illustrate, the Kaplan Meier curve was created using the median SMG as a cutoff. Analyses were conducted using SAS statistical software version 9.4 (Cary, NC).

Results

Study population

Forty patients were identified who met eligibility criteria (see Supplementary Figure 1). Patients, treatment and toxicity characteristics described in Table 1. The median age was 55 years (range 34 – 80) and the mean disease free interval was 3.8 years. All patients were chemotherapy-free for at least 6 months since the adjuvant chemotherapy. Metastatic diagnosis period was 2003–2015. Median time from CT scan to chemotherapy initiation was 20 days [range 2–36 days prior]. Median length of follow up for the survivors was 1.9 years. Patient characteristics are shown in Table 1. Chemotherapy regimens are shown in table 1 and included: paclitaxel (N=31 weekly schedule, 26 patients received 80 mg/m^2, 4 patients received 90 mg/m^2 on clinical trial, and one patient was dose reduced 20% (64 mg/m^2) because of liver function test (LFT) abnormality), docetaxel (N=4, two received 75 mg/m^2,

one 60 mg/m^2 (dose reduced due to high LFTs) and one 100 mg/m^2 at first dose-every 3 weeks), and nab-paclitaxel (N=5, one patient received 260 mg/m^2, one patient received 25 % dose reduction (195 mg/m^2) from first dose because of her age and performance status-every 3 weeks, two received 100 mg/m^2 weekly dose, and one received 175 mg/m^2 every two weeks on clinical trial).

Fifteen patients (37.5%) received biological therapy in addition to a taxane (trastuzumab (N=11) and pertuzumab/trastuzumab (N=4)). Ten patients (25%) received the anti-angiogenesis inhibitor bevacizumab with a taxane. Of the 40 eligible patients, 58% were identified as sarcopenic (Table 1 for baseline body composition metrics). No grade 5 (death) toxicity was recorded.

Body composition as a predictor of grade 3–4 toxicity

Sixteen patients (40%) developed grade 3–4 toxicity during cycles 1–3. Of note, none of the toxicities recorded are likely due to the biologic agent used with the corresponding taxane. There was one patient with diarrhea receiving trastuzumab but none of the four pertuzumab treated patients had grade 3 or 4 diarrhea. Sarcopenic patients experienced significantly more grade 3–4 toxicity compared to non-sarcopenic patients (figure 2A, 57% vs 18%, p=0.02). Patients who had grade 3–4 toxicity during cycles 1–3 had significantly lower SMG than those who did not (figure 2B, mean 1046 vs 1385, p=0.04) and also lower SMD (26.6 v 31.9, p=0.010). BMI, BSA, and estimated lean body mass (LBM), were not associated with cycle 1–3 toxicity.

Body composition as a predictor of hospitalizations

Nine patients were hospitalized due to treatment-related toxicity and all were sarcopenic. Hospitalizations were significantly associated with low lean body mass (34.7 vs 40.6, p=0.03), low SMD (23.3 vs 31.7, p=0.03), and low SMG (862 vs 1362, p=0.01).

Body composition as a predictor of any adverse event

Adverse events (hospitalization, grade 3–4 toxicity, dose reductions, or delay) occurred in 23 patients, of which 17 (74%) were sarcopenic. Sarcopenia was significantly associated with any adverse event (74% sarcopenic vs 35% not sarcopenic, p=0.02). Lower SMG had a borderline significant association with any adverse event (1115 vs 1431, p=0.06). All toxicity events summarized in table 2.

Body composition as a predictor of time to treatment failure and overall survival

Median TTF for the entire sample was 6.5 months (95% CI: 3.4 – 9.2 months), with no significant difference between sarcopenic and non-sarcopenic patients (median 6.2 vs 9.2 months, p=0.18; see table 3). BMI, BSA, LBM, and SMD were also not associated with time to treatment failure. However, SMG was significant and for each 100 unit increase, a patient's risk of treatment failure decreased by 9% (Figure 3A, HR=0.91, 95% CI 0.84–0.99, p=0.03). Median OS for the entire sample was 32.3 months (95% CI: 23.4–40.3 months), with borderline significant difference between sarcopenic and non-sarcopenic patients (median 30 vs 40.3 months, p=0.07). BMI, BSA, LBM, and SMD were not associated with differences in OS. Low SMG had a borderline significant association with shorter survival

(Figure 3B) and for each 100 unit increase a patient's risk of death decreased by 7% (HR=0.93, 95% CI 0.87–1.00, p=0.07).

Discussion

This study found that body composition measures varied widely in women with MBC receiving first line taxane-based chemotherapy regimens, and that body composition and skeletal muscle measures could have important implications for treatment decisions. Sarcopenic patients had 3 times more grade 3–4 toxicity and twice the number of adverse events. Of note all treatment related hospitalizations (N=9) were in sarcopenic patients. SMG, a novel measure of body composition, was significantly associated with grade 3–4 toxicity, hospitalizations related to treatment toxicity, and TTF. SMG was also borderline significant predictor of adverse events and overall survival. LBM was significantly associated with hospitalizations while BMI and BSA were not predictive of toxicity. In our sample of patients none were underweight [BMI<=18.5] indicating that sarcopenia and SMG are independent of BMI. Of note, the number of hospitalizations in our study was higher than excepted (19). Most of the data regarding hospitalizations from taxanes toxicity come from randomized trials with strict eligibility and performance status criteria. These patients are not representative of those seen in general oncology practice.

Our results are in line with findings reported in other studies, such as Prado et al, showing higher toxicity and shorter time to progression in sarcopenic MBC patients receiving capecitabine who had failed anthracycline and/or taxane treatment [(7)]. Unlike in our study where we focused on more severe toxicity grades, Prado and colleagues included grade 2 toxicity in her outcome assessments. Similarly, Tamandl *et al* showed that low skeletal muscle attenuation was associated with impaired OS (HR =1.91, 95 % CI 1.12–3.28, p=0.019) in gastro-esophageal cancer [(16)] and a Dutch study in metastatic colorectal cancer also found similar results (HR=2.38 95% CI- 1.16–4.87 p=0.018)(17). Our study provides an innovative contribution to the literature by taking into account not only the quantity of the muscle (SMI) but also the muscle composition "quality" (SMD) and using a new novel body composition parameter that combines the two -- SMG. We believe that this measure may prove to be the most important, and as it combines two measures of muscle that have been shown to be independent predictors of outcomes in other studies.

There is growing interest in exploring the relationship between body composition, toxicity, and treatment outcomes in early (20–22) and advanced (7, 23–27) cancer patients. With simplified and standardized image analysis of CT images, these measures could be easily performed by radiologist using existing CT images obtained as part of routine care in both the academic and community setting. Sarcopenia and other body composition measures may provide independent information for assessing treatment risks and guiding disease management with potential dosing implications (28, 29). Typically, physicians dose patients based on body surface area (30), but recently there is a growing evidence that LBM is better correlated with drug clearance pharmacokinetics than BSA (31). The desire to select chemotherapy doses that maximize the therapeutic index has existed for a long time (32), but until recently no simple, readily available tools existed to do so. Our research and that of others suggests that sarcopenia as measured from routine CT images obtained as part of

staging or to evaluate treatment response might perform this role (21, 33). Using body composition measurements to individualize dosing could represent a dramatic step forward into the personalized medicine era

Understanding the importance of sarcopenia and body composition in patients with cancer also highlights the need for timely interventions to increase or prevent further loss of muscle mass during treatment and in survivorship. Intervention research to date has focused on exercise (34–36), vitamin D (37), and omega-3 fatty acid dietary supplementation (38). Other new therapeutic approaches including melanocortin-4 receptor antagonists (39) and IL-6 antagonism (40) are also under investigation. Recently, a randomized controlled trial in lung cancer that compared anamorelin a novel ghrelin-receptor agonist to placebo showed significant LBM gain in the intervention arm (41). Further research on the impact of these interventions on toxicity and efficacy outcomes and how to incorporate them into oncology practice is needed.

Our study is not without limitations. First we had a small sample size, which likely limited our statistical power to detect significant differences in some of the body composition measurements and outcomes. Second, many of our patients received concurrent treatment with biologic agents (trastuzumab and bevacizumab). This may have affected our results, since biologics have toxicity profiles that differ from chemotherapy. However, the toxicities reported in study are highly unlikely to be due to the addition of biologic therapy as noted in the results section above. Another limitation is combining different taxane regimens that -- although they have a similar mechanism of action -- have different pharmacokinetics and different toxicity profiles. Given this concern, we performed a sensitivity analysis of patients that received paclitaxel only (N=31). We found that sarcopenia remained a significant predictor for grade 3–4 toxicity (p=0.05) and any adverse event (p=0.03), and was borderline for hospitalizations (6 patients that received paclitaxel were hospitalized due to toxicity and all were sarcopenic, p=0.07). SMG became borderline significant with hospitalization (SMG 1362 vs 908 AU, p=0.06), any adverse event (1448 vs 1130 AU, p=0.10), and grade 3–4 toxicity (1388 vs 1067 AU, p=0.11). Due to differences in pharmacokinetics and toxicity profiles of taxanes, we encourage future studies to explore each of these drugs separately.

To the best of our knowledge this is the first study that examines the effect of body composition measures in metastatic breast cancer treated with taxanes. Our results show that body composition is correlated with cancer and toxicity outcomes and suggest that patients with low muscle mass or LBM have more treatment related toxicity, while BSA has no correlation with toxicities. Using existing imaging and readily available software, skeletal muscle mass assessments could be incorporated into the clinical setting. Further research using body composition assessments to develop novel dosing strategies as well as targeting effective interventions is necessary in patients with cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like thank Dr. Vickie Baracos, University of Alberta, for generously providing her CT image analysis software, Ms. Amy Garrett for her great help in study coordination, and Dr. Hyeon Yu, UNC Department of Radiology, for training the team on CT image analysis.

Funding: This work is supported by the Breast Cancer Research Foundation, New York, N.Y. and the UNC Lineberger Comprehensive Cancer Center. The research supported in part by the Medical Student Training in Aging Research (MSTAR) program (NIA 2-T35-AG038047-06), through the American Federation for Aging Research (AFAR), and by the UNC Oncology Clinical Translational Research Training Program (NCI 5K12CA120780-07). Dr. Shachar gratefully acknowledges support from the Friends of Rambam Medical Center and The J & G Zukier Medical Fund Donation, Haifa, Israel. Database support was provided in part through Komen Foundation Grant SAC110044 awarded to Dr. E. Claire Dees. REDCap use award to the North Carolina Translational & Clinical Sciences Institute (1UL1TR001111), Clinical and Translational Science Award program of the National Center for Advancing Translational Sciences, National Institutes of Health. UNC Oncology Clinical Translational Research Training Program (NCI 5K12CA120780-07). The authors do not have a financial relationship with either organization. The funding sources had no involvement in study design, collection of data, data interpretation, or writing of this report.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015; 65:87–108. [PubMed: 25651787]
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a cancer journal for clinicians. 2016; 66:7–30. [PubMed: 26742998]
3. Veronesi U, Marubini E, Del Vecchio M, Manzari A, Andreola S, Greco M, et al. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. Journal of the National Cancer Institute. 1995; 87:19–27. [PubMed: 7666458]
4. Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). Breast (Edinburgh, Scotland). 2012; 21:242–52.
5. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. American journal of epidemiology. 1998; 147:755–63. [PubMed: 9554417]
6. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. European journal of cancer. 2016; 57:58–67. [PubMed: 26882087]
7. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clinical cancer research: an official journal of the American Association for Cancer Research. 2009; 15:2920–6. [PubMed: 19351764]
8. Wong AL, Seng KY, Ong EM, Wang LZ, Oscar H, Cordero MT, et al. Body fat composition impacts the hematologic toxicities and pharmacokinetics of doxorubicin in Asian breast cancer patients. Breast cancer research and treatment. 2014; 144:143–52. [PubMed: 24481679]
9. Nabholtz JM, Gelmon K, Bontenbal M, Spielmann M, Catimel G, Conte P, et al. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1996; 14:1858–67. [PubMed: 8656254]
10. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. The New England journal of medicine. 2015; 372:724–34. [PubMed: 25693012]
11. Institute NC. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 data files. 2015. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html
12. Popuri K, Cobzas D, Esfandiari N, Baracos V, Jagersand M. Body Composition Assessment in Axial CT Images using FEM-based Automatic Segmentation of Skeletal Muscle. IEEE Transactions on Medical Imaging. 2015; 35:512–20. [PubMed: 26415164]

13. Chung, H.Cobzas, D.Birdsell, L.Lieffers, J., Baracos, V., editors. SPIE Medical Imaging; 2009. International Society for Optics and Photonics; Automated segmentation of muscle and adipose tissue on CT images for human body composition analysis.
14. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2013; 31:1539–47. [PubMed: 23530101]
15. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta physiologica (Oxford, England). 2014; 210:489–97.
16. Tamandl D, Paireder M, Asari R, Baltzer PA, Schoppmann SF, Ba-Ssalamah A. Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected oesophageal or gastro-oesophageal junction cancer. European radiology. 2016; 26:1359–67. [PubMed: 26334504]
17. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, den Braver NR, Berkhof J, Langius JA, et al. Loss of Muscle Mass During Chemotherapy Is Predictive for Poor Survival of Patients With Metastatic Colorectal Cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2016; 34:1339–44. [PubMed: 26903572]
18. Weinberg M, Shachar S, Deal A, Williams G, Nyrop K, Alston S, et al. Characterization of skeletal muscle and body mass indices in younger and older women with stage II and III breast cancer. J Am Geriatr Soc. 2016; (supplement):S86.
19. Alsharedi M, Gress T, Dotson J, Elmsherghi N, Tirona MT. Comparison of toxicity profile and tolerability between two standard of care paclitaxel-based adjuvant chemotherapy regimens in breast cancer. Medical oncology (Northwood, London, England). 2016; 33:27.
20. Prado CM, Lima IS, Baracos VE, Bies RR, McCargar LJ, Reiman T, et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. Cancer chemotherapy and pharmacology. 2011; 67:93–101. [PubMed: 20204364]
21. Prado CM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clinical cancer research: an official journal of the American Association for Cancer Research. 2007; 13:3264–8. [PubMed: 17545532]
22. Tan BH, Brammer K, Randhawa N, Welch NT, Parsons SL, James EJ, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015; 41:333–8.
23. Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Annals of oncology: official journal of the European Society for Medical Oncology/ESMO. 2010; 21:1594–8.
24. Barret M, Antoun S, Dalban C, Malka D, Mansourbakht T, Zaanan A, et al. Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. Nutrition and cancer. 2014; 66:583–9. [PubMed: 24707897]
25. Cushen SJ, Power DG, Teo MY, Maceneaney P, Maher MM, McDermott R, et al. Body Composition by Computed Tomography as a Predictor of Toxicity in Patients With Renal Cell Carcinoma Treated With Sunitinib. American journal of clinical oncology. 2014 Epub Ahead of Print.
26. Huillard O, Mir O, Peyromaure M, Tlemsani C, Giroux J, Boudou-Rouquette P, et al. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. British journal of cancer. 2013; 108:1034–41. [PubMed: 23462722]
27. Massicotte MH, Borget I, Broutin S, Baracos VE, Leboulleux S, Baudin E, et al. Body composition variation and impact of low skeletal muscle mass in patients with advanced medullary thyroid carcinoma treated with vandetanib: results from a placebo-controlled study. The Journal of clinical endocrinology and metabolism. 2013; 98:2401–8. [PubMed: 23543666]

28. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Seminars in cell & developmental biology. 2016; 54:2–10. [PubMed: 26343952]
29. Hubbard JM, Cohen HJ, Muss HB. Incorporating biomarkers into cancer and aging research. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2014; 32:2611–6. [PubMed: 25071114]
30. Du BD, Du BE. Clinical calorimetry: Tenth paper a formula to estimate the approximate surface area if height and weight be known. Archives of Internal Medicine. 1916; XVII:863–71.
31. McLeay SC, Morrish GA, Kirkpatrick CM, Green B. The relationship between drug clearance and body size: systematic review and meta-analysis of the literature published from 2000 to 2007. Clinical pharmacokinetics. 2012; 51:319–30. [PubMed: 22439649]
32. Ratain MJ. Body-surface area as a basis for dosing of anticancer agents: science, myth, or habit? Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 1998; 16:2297–8. [PubMed: 9667242]
33. Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. The Lancet Oncology. 2008; 9:629–35. [PubMed: 18539529]
34. Maddocks M, Murton AJ, Wilcock A. Improving muscle mass and function in cachexia: non-drug approaches. Current opinion in supportive and palliative care. 2011; 5:361–4. [PubMed: 21934503]
35. Argiles JM, Busquets S, Lopez-Soriano FJ, Costelli P, Penna F. Are there any benefits of exercise training in cancer cachexia? Journal of cachexia, sarcopenia and muscle. 2012; 3:73–6.
36. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cachexia and sarcopenia: mechanisms and potential targets for intervention. Current opinion in pharmacology. 2015; 22:100–6. [PubMed: 25974750]
37. Kung T, Springer J, Doehner W, Anker SD, von Haehling S. Novel treatment approaches to cachexia and sarcopenia: highlights from the 5th Cachexia Conference. Expert opinion on investigational drugs. 2010; 19:579–85. [PubMed: 20367196]
38. Di Girolamo FG, Situlin R, Mazzucco S, Valentini R, Toigo G, Biolo G. Omega-3 fatty acids and protein metabolism: enhancement of anabolic interventions for sarcopenia. Current opinion in clinical nutrition and metabolic care. 2014; 17:145–50. [PubMed: 24500439]
39. Dallmann R, Weyermann P, Anklin C, Boroff M, Bray-French K, Cardel B, et al. The orally active melanocortin-4 receptor antagonist BL-6020/979: a promising candidate for the treatment of cancer cachexia. Journal of cachexia, sarcopenia and muscle. 2011; 2:163–74.
40. Berardi E, Annibali D, Cassano M, Crippa S, Sampaolesi M. Molecular and cell-based therapies for muscle degenerations: a road under construction. Frontiers in physiology. 2014; 5:119. [PubMed: 24782779]
41. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. The Lancet Oncology. 2016; 17:519–31. [PubMed: 26906526]

STATEMENT OF TRANSLATIONAL RELEVANCE

This paper contains a number of novel concepts regarding chemotherapy toxicity and represents the first study of the impact of skeletal muscle measures in patients with metastatic breast cancer receiving taxane chemotherapy. Muscle measures have an emerging role in predicting treatment toxicity and survival in patients with cancer. Our results shows that sarcopenic (low muscle mass) patients have more treatment related adverse outcomes such as grade 3–4 CTCAE toxicities, hospitalizations, and other adverse events. Furthermore, our work is the first to demonstrate the innovative combination of muscle mass (quantity) and radiodensity (quality) as a predictor to chemotherapy outcome. Our results suggest that muscle measurements obtained from computed tomography (CT) images performed for routine oncologic care could be used to individualize chemotherapy dosing better than body surface area.

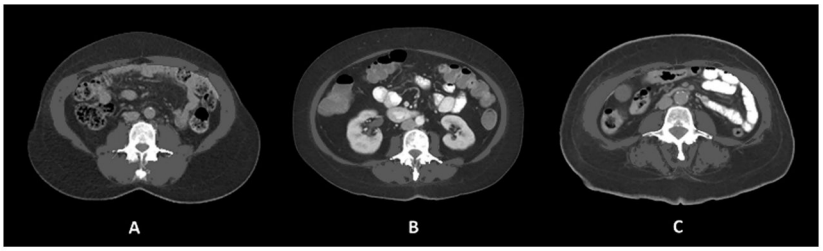

Image	Body mass index (kg/m^2)	Skeletal muscle index (cm^2/m^2)	Skeletal muscle density (HU)	Skeletal muscle gauge (AU)
A	32	51	36	1836
B	32	36	31	1116
C	32	46	22	1012

Figure 1.

Three examples of body composition, all BMI = 32

A: normal SMI and high SMG; **B**: sarcopenic and low SMG; **C**: normal SMI and low SMG; Abbreviations: AU – Arbitrary Units; HU - Hounsfield Units; SMI - Skeletal Muscle Index; SMG - Skeletal Muscle gauge

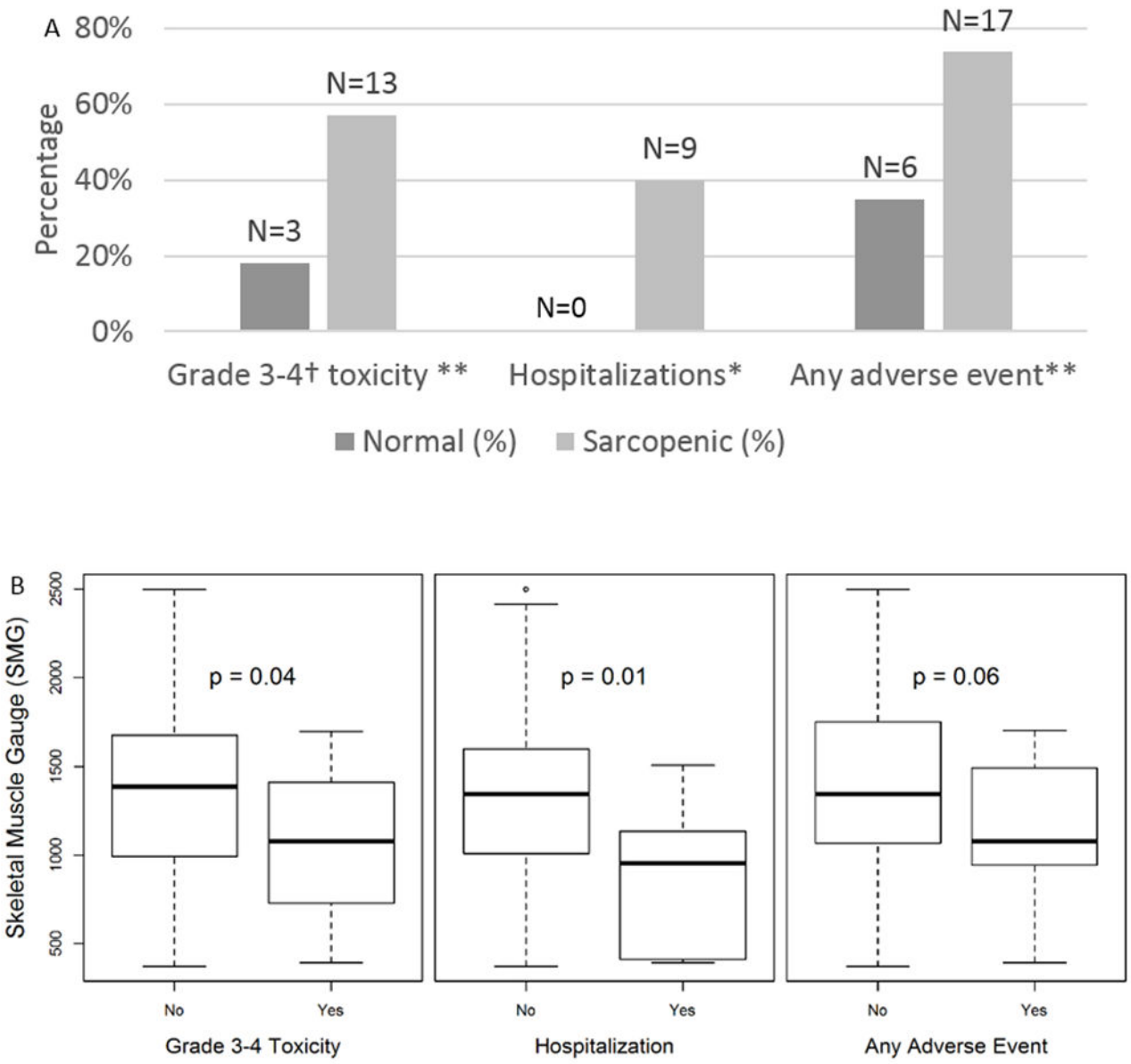

Figure 2.

Skeletal muscle measures and adverse outcomes

A –Sarcopenia and adverse outcomes; **B** –Skeletal muscle gauge and adverse outcomes

† Grade 3–4 toxicity by CTCAE(11) in cycles 1–3 of chemotherapy; *p =0.005; **p =0.02

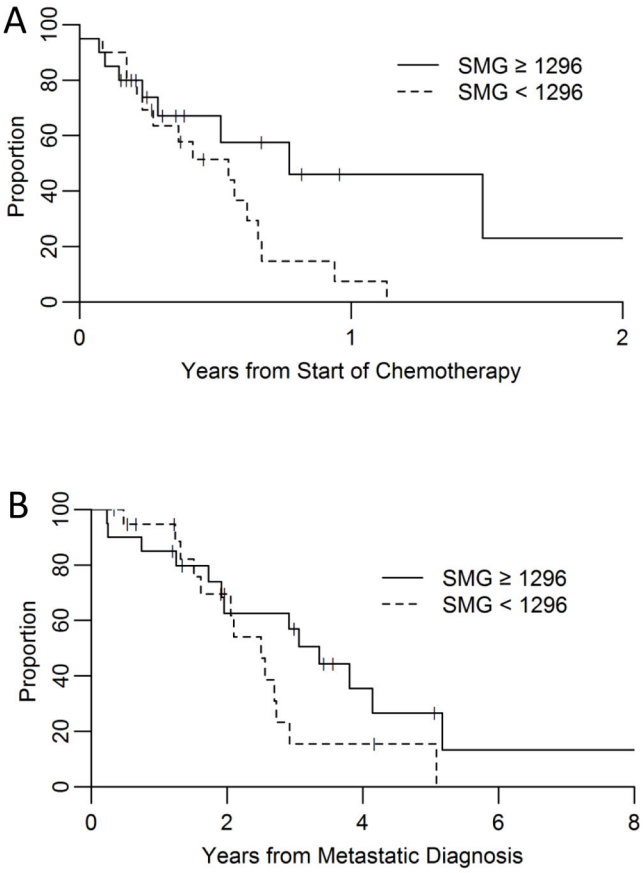

Figure 3.

Skeletal muscle measures and time to event

A- Skeletal muscle gauge and time to treatment failure; **B**- Skeletal muscle gauge and overall survival

Time to treatment failure was defined as days from start to end of chemotherapy whether stopped for either toxicity or tumor progression.

The *p*-value for SMG as a continuous variable is 0.03 for time to treatment failure and 0.07 for overall survival.

Abbreviations: SMG- Skeletal Mass Gauge

Table 1

Patients characteristics, body composition measures, and toxicity events (N=40)

	N/mean (SD)	%
Age at metastatic diagnosis years	56 (11.7)	
Age < 65 years	33	83
Disease free interval (years)	3.8 (5.2)	
Subtype		
HR positive/HER2 negative	15	38
HER2 positive	14	36
HR negative/HER2 negative	10	26
Sites of metastasis at metastatic diagnosis		
Bone	25	62
Liver	12	30
Lung	5	12
Chemotherapy		
Paclitaxel	31	78
Docetaxel	4	10
Nab-paclitaxel	5	12
Biological therapy		
Trastuzumab	11	27
Pertuzumab/Trastuzumab	4	10
Bevacizumab	10	25
Chemotherapy		
Paclitaxel	31	78
Docetaxel	4	10
Nab-paclitaxel	5	12
Body composition measures		
Sarcopenia	23 (58)	
Skeletal Muscle Index (cm^2/m^2)	41.2 (9.1)	
Skeletal Muscle Density (Hounsfield Units)	29.8 (10)	
Skeletal Muscle Gauge (Arbitrary Units)	1249 (522)	
Body Mass Index (kg/m^2)	29.0 (7.3)	
Body Surface Area (m^2)	1.87 (0.26)	
Lean Body Mass[a] (kg)	39.3 (7.2)	
Toxicity events[b]		
All grade 3–4 Cycles 1–3	16	40
Grade 3–4 neutropenia	7	17.5
Grade 3–4 anemia	3	7.5
Grade 3–4 gastrointestinal toxicity	5	12.5

	N/mean (SD)	%
Grade 3–4 neuropathy	6	15
Grade 3–4 neutropenic fever	2	5
Hospitalizations		
All hospitalizations	9	23
Infection	5	13
Gastrointestinal toxicity	2	5
Neutropenic fever	2	5
Dose reductions	10	25
Dose delays	11	28
Any adverse event[c]	23	58

[a] Estimated Lean Body Mass(7);

[b] Grade 3–4 toxicity by CTCAE(11) in cycles 1–3 of chemotherapy;

[c] Any adverse event includes hospitalization, grade 3–4 toxicity, dose reductions, or delay

Abbreviations: HR- hormone receptor; HER2- human epidermal growth factor Receptor 2; SD- standard deviation

Table 2

Toxicity and mean body composition measures

Variable (mean)	Cycles 1–3 toxicity[b]			Hospitalization			Any adverse event		
	No	Yes	*p* value	No	Yes	*p* value	No	Yes	*p* value
Skeletal muscle density (HU)	31.94	26.57	0.10	31.66	23.34	**0.03**	32.34	27.9	0.17
Skeletal muscle gauge (AU)	1385	1046	**0.04**	1362	862	**0.01**	1431	1115	**0.06**
Body mass index (kg/m^2)	27.65	31.06	0.15	28.55	30.61	0.47	27.58	30.04	0.29
Body surface area (m^2)	1.84	1.93	0.30	1.86	1.92	0.57	1.83	1.90	0.41
Lean body mass[a] (Kg)	40.68	37.14	0.13	40.61	34.63	**0.03**	41.16	37.87	0.16

[a] Estimated Lean Body Mass(7);

[b] Grade 3–4 toxicity by CTCAE(11) in cycles 1–3 of chemotherapy

Abbreviations: AU – Arbitrary Units; HU - Hounsfield Units

Table 3

Hazard Ratios for Time to Treatment Failure and Overall Survival by body composition measures

	Time To Treatment Failure[a]	*p* value	Overall Survival	*p* value
Sarcopenia (yes/no)	1.78	0.18	2.21	0.07
Skeletal muscle density (HU)	0.97	0.10	0.98	0.27
Skeletal muscle gauge (100 AU)	**0.91**	**0.03**	**0.93**	**0.07**
Body mass index (kg/m^2)	1.03	0.36	0.98	0.55
Body surface area (m^2)	3.65	0.10	0.61	0.59
Lean body mass (Kg)	0.98	0.39	0.95	0.10

[a]Time to treatment failure was defined as days from start to end of chemotherapy whether stopped for either toxicity or tumor progression

Abbreviations: HU - Hounsfield Units; AU – Arbitrary Units.